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14. ABSTRACT

Our efforts over this reporting period (April 1, 2011 to March 31, 2012) were on proposing one new concept , finishing development of another concept and accruing to six DOD-PCCTC trials including two that stem from major contributions by our group.

c11-089 is a randomized, gene fusion-stratified Phase II trial investigating Abiraterone ± ABT-888 in mCRPC. The hypothesis of the trial is that therapeutic targeting based on ETS gene fusions can improve disease response rates in patients with these molecular subtypes of cancer and in patients with ETS fusion-positive tumors, the targeting of the promoter and the transcription factor of the ETS fusion is more effective than targeting a single aspect of the fusion. The TMPRSS2-ETS gene fusion (discovered by a UM researcher) is present in over 50% of all prostate cancers (ERG is the most common fusion partner of the ETS genes with TMPRSS2). The biomarker-stratified design will be used to determine if there is a response difference between treatments by ETS gene fusion-positive and fusion-negative strata. UM will be the lead site for this trial with the Univ. of Chicago N01 Phase II consortium as the coordinating center. Ten comprehensive cancer centers (six of which are DOD-PCCTC member sites) will be participating in this trial, with interest from other outside institutions as well as possibly an additional PCCTC member site. This trial was selected to be part of the Stand Up to Cancer (SU2C) – Prostate Cancer Dream Team Translational Cancer Research Grant (AACR/PCF) This trial was activated at our site by the NCI on 4/18/2012.

c11-080 is a multi-institutional Phase I and biomarker study of Everolimus combined with hormonal and radiation therapy for high risk prostate cancer introduced to the PCCTC by Dr. Daniel Hamstra who is the PI for this study which was based on pre-clinical work supported by a Young Investigator Award from the Prostate Cancer Foundation (PCF). The clinical trial is being supported by an ASCO Career Development Award. Two other PCCTC institutions will be participating in this study. Due to delays caused by Everolimus availability, we now expect to activate this trial in May 2012. UM will act as the coordinating center for this trial.

c11-079 is the Phase II expansion cohort of the randomized discontinuation trial of XL184 in solid tumors introduced to the PCCTC by Dr. David Smith. Dr. Smith and Dr. Hussain were involved in designing the expansion phase of this study with the sponsor. Seven other PCCTC institutions are participating in this trial.

15. SUBJECT TERMS
prostate cancer, phase I/II, phase II, clinical consortium

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B. **c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Maha Hussain**, Michael Anthony Carducci, Susan F. Slovin, Jeremy Paul Cetnar, Jiang Qian, Evelyn Mary McKeegan, Elizabeth Litvinovich, Brenda Chyla, Robert Hetman, Bhardwaj Desai, Vincent L. Giranda, Joshi J. Alumkal. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224).**

C. **c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial.** . S. Antonarakis, E. I. Heath, **D. C. Smith**, D. E. Rathkopf, A. L. Blackford, D. C. Danila, S. King, A. Frost, M. A. Carducci. **American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). UMICH - co-author.**

D. **c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. M. Hussain,** M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara, C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, **D. C. Smith. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516).**

E. **c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen**

(PSA): Results of a phase 2 study. Hussain, M., Corn, P., Michaelson, D., Hammers, H., Alumkal, J., Ryan, C., Bruce, J., Moran, S., Mortimer, P., Lee, S.Y., George, D. Abstract and poster presented by Dr. Hussain at the **27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012 (abstract and poster #124).**

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F. **c09-024 - A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study.** JE Ward, T Karrison, G Chatta, **M Hussain**, D Shevrin, RZ Szmulewitz, PH O'Donnell, WM Stadler and EM Posadas. **Prostate Cancer and Prostatic Diseases (2012) 15, 87–92.**

INTRODUCTION
University of Michigan Comprehensive Cancer Center

The Prostate Oncology Program is an interdisciplinary group of 37 laboratory, translational and clinical researchers from 11 departments and four schools with over $13 million in annual direct research support. The Prostate Oncology Program continues its primary mission of translating basic and clinical discoveries in prostate cancer into effective medical solutions. The program includes a Prostate SPORE, a PO1 on the Biology of Prostate Cancer Bone Metastasis, a Department of Defense funded Prostate Cancer Clinical trials Consortium site (DOD-PCCTC), a prostate-focused Early Disease Research Network (EDRN) site, a NIDDK training grant in Clinical and Translational Research Training in Urology (T32) and a N01 contract with CTEP (University of Chicago – Early Therapeutics Development with Phase II emphasis group). The Program is committed to creating and sustaining a multidisciplinary environment for basic and clinical researchers studying prostate cancer. The success of this multidisciplinary environment is reflected in the number of intra- and inter-programmatic publications published by the group in the last five years (The program has over 700 publications, of which 140 publications are in high impact journals (Impact factor >7.5) [and of these 21% are intra-programmatic and 23% are inter-programmatic]. The objective of the Prostate Oncology Program is to understand the biology of prostate cancer and to use this information to develop new tools for the detection, diagnosis, prevention, and treatment of prostate cancer. This objective is being pursued through investigations addressing four over-arching aims: Aim 1: To investigate the genetic and epigenetic events that contribute to malignant transformation. Aim 2: To characterize aberrations in cellular biology and function in urological cancers. Aim 3: To translate basic scientific discoveries to develop new biomarkers and therapies in urological cancers. Aim 4: To evaluate clinical outcomes with the purpose of guiding therapy development while reducing cancer-related mortality as well as cancer and therapy-associated morbidities. The goals of the Prostate and Urological Oncology Program at the University of Michigan reverberates that of the Department of Defense's: to combine the efforts of the nation's leading investigators and scientists to test novel therapeutic interventions that will ultimately decrease the overall impact of the disease. That is, to prevent, to detect, and to cure prostate cancer and to improve the quality of life for individuals living with prostate cancer and their families.

The Prostate Oncology Program (under the co-leadership of Dr. Hussain and Dr. Evan Keller) was ranked Exceptional by the NCI scientific reviewers as part of our recent Comprehensive Cancer Center NCI core grant renewal.

ANNUAL REPORT — BODY

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan as a clinical consortium research site during the reporting period (04-01-2011 to 03-31-2012) of the DOD-PCCTC grant are summarized in this report. The focus of the University of Michigan during the period of DOD-PCCTC funding has been to continue work with the consortium investigators and outside sponsors, including the NCI, to bring novel research to the DOD-PCCTC, to continue to actively accrue to DOD-PCCTC trials, and to expand collaboration with other nonconsortium institutions. At the end of the third year of DOD-PCCTC funding from the new 2009 Clinical Consortium Award, six studies with novel drugs have been introduced to the DOD-PCCTC by the University of Michigan. One of these trials (c11-089, ABT-888/Abi/Gene fusion) was introduced to the DOD-PCCTC during the current reporting period. The trials are as follows:

c09-031, ABT-888, LOI circulated 2/25/09
c09-044, TAK-700, LOI circulated 7/09/09
c09-057, EMD 525797, LOI circulated 12/11/09 and 4/28/10
c11-079, XL184, LOI circulated 1/5/11
c11-080, Everolimus, LOI circulated 2/10/11
c11-089, ABT-888/Abi/Gene Fusion, LOI circulated 8/10/11

Three trials have been completed at the end of this third year of funding and are undergoing final analysis of clinical and biological samples. These trials and their closure dates are listed below.

c08-001, Imclone, closed to accrual 11/20/2009 (overall study closure 9/30/2011)
c09-031, ABT-888, closed to accrual 10/22/2010
c09-044, TAK700, closed to accrual 6/17/2011

Two trials (c09-044, TAK-700) and (c10-073, Cediranib/Dasatinib) closed during this reporting period. Several abstracts were presented at national and international meetings from the completed trials. We continue to maintain and improve the necessary infrastructure to facilitate the execution of multicenter trials; a process that includes data sharing, opening and accruing to consortium trials, disseminating initial findings from PCCTC-DOD trials to the Consortium and larger research community, as well as introducing important and novel translational clinical trials to the DOD-PCCTC for member participation.

Going forward during this new grant period, we will continue to introduce new concepts based on data generated by our scientists taking advantage of the DOD-PCCTC strengths both from an intellectual scientific perspective and accrual abilities, participate in consortium studies and complete analysis and reporting of the University of Michigan-led completed trials.

Administrative Infrastructure

The investigators and research personnel that are funded, in part, by the Department of Defense grant can be found in Table 1. Currently they include five medical oncologists, one radiologist, three data managers, one biostatistician, two clinical research nurses, one study coordinator and one study administrator. A new faculty member was introduced to our group, Dr. Ajjai Alva, a medical oncologist with an effective start date on this award of February 1, 2012.

Table 1. University of Michigan Personnel

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A list of personnel who received any pay for the research efforts described in this report appears

in Supporting Data (**Table F**).

As a consortium research site, the University of Michigan fulfilled the following tasks:

Task #1: Conduct the clinical trials along the lines of research outlined in the proposal. Patient accrual and sample collection (Months 1-48).

Includes patient accrual and biological samples collection for: 1. Studies that have been activated in the final quarter of the previous funding period and 2. All new studies that will be proposed for this funding period. This is for studies initiated both by the University of Michigan and other consortium sites. Outlined in the initial proposal were five research objectives relating to this first task in the Statement of Work.

1. Introduce and accrue to new clinical trials.
2. Participate and accrue to other member's trials with the expectation that patient contribution to trials from other sites shall constitute at least 20% of the total number of patients our site contributes to all trials.
3. Data collection and biologic sample collection.
4. Accrue a minimum of 35 patients per year to consortium trials annually with every effort made to expand this enrollment to 50 patients or more annually. At least 5% of all accrued patients, independently or in partnership with other consortium or non-consortium institutions, will be from disproportionately affected populations.
5. Present at least one clinical trial to the consortium per year with the expectation of presenting two or more clinical trials to the consortium per year.
6. We will be constantly monitoring the quality of the data collected using previously implemented Consortium standard operating procedures in addition to timely data sharing and reporting.
7. Submit and present interim or final reports on completed trials as appropriate at national meetings and symposia.
8. We will adhere to all consortium procedures and fulfill our University of Michigan IRB requirements for the conduct of clinical trials and the protection of human subjects.
9. Participate in all consortium activities and committees.
10. Take an active role in helping to implement the Coordinating Center's plan for the financial self-sufficiency of the consortium by the end of the award period.
11. Prepare, submit and present where appropriate the required semi-annual briefings for the EAB and USAMRMC staff at consortium meetings; submit annual written progress reports and a final written comprehensive report to the USAMRMC .

Table 2 presents all the DOD-PCCTC trials that were open for accrual during this reporting period at the University of Michigan. During this current reporting period we have accrued 20 patients to consortium trials. Table C and D show that we have accrued approximately 5% of our accruals for this reporting period from disproportionately affected populations (DAP). Table E shows that our patient contribution to trials from other sites constituted 40% of the total number of patients our site contributed to all trials. During this reporting period we accrued 12 patients to our phase II biomarker trial SWOG S0925 (b11-011) and 8 patients to the OGX-11-10 (b11-010) biomarker trial (see Table 2).
Table 4 presents all the DOD-PCCTC trials that are either open for accrual or are in the process of being activated for accrual at the University of Michigan. Each trial's specific area of focus as related to Objective #1 can be found in the first column of Table 4. From this table, it is apparent that the University of Michigan is successfully working towards accomplishing Objective 1, carrying out a wide range of clinical trials to develop more effective systemic therapies for prostate cancer.

With regards to objective 10, the University of Michigan has developed and maintained successful collaborative efforts. The University of Michigan has maintained a successful membership in the University of Chicago N01 Phase II Consortium sponsored by the Cancer Therapy Evaluation Program (CTEP), of the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI) (http://www.cancer.gov/). The major

emphasis of this consortium is on Phase II studies and pilot protocols that explore promising single agent and combination therapies, and high priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting. These groups provide a valuable addition to our group's other diverse collaborative research networks including: the PCCTC, and National cooperative groups (SWOG, RTOG, ECOG) and can particularly synergize with the DOD-PCCTC. Successful collaborations, we believe, are the first step towards implementing the Coordinating Center's plan for the financial self-sufficiency of the consortium by the end of the award period.

Table 2: Total and current reporting period University of Michigan Accruals to DOD-PCCTC Trials

DOD Number	PROTOCOL TITLE	UM PI	Total UM Accrual	UM Accrual Apr 01 2011– Mar 31 2012
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	**Dr. Hussain**	4	4
c09-044	A Phase 2 Multicenter Open-label Study Evaluating the Safety and Efficacy of TAK-700 in Patients with Nonmetastatic Castration-resistant Prostate Cancer (CRPC) and a Rising Prostate-specific Antigen (PSA)	**Dr. Hussain**	6	1
c10-071	A Phase II study of single-agent tesetaxel in chemotherapy-naive and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	**Dr. Hussain**	6	5
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	**Dr. Smith**	30	7
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	**Dr. Smith**	3	3
c10-072	An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Metastatic Castration-Resistant Prostate Cancer	**Dr. Smith**	1	0
Totals			**50**	**20**
Biomarker Trials				
DOD Number	**PROTOCOL TITLE**	**UM PI**	**Total UM Accrual**	**UM Accrual Apr 01 2010– Mar 31 2011**
b11-011	A Randomized Phase II Study of Combined Androgen Deprivation Versus Combined Androgen Deprivation with IMC-A12 for Patients with New Hormone Sensitive Metastatic Prostate Cancer (SWOG 0925)	**Dr. Hussain**	13	12
b11-010	A Randomized Phase 3 Study Comparing Standard First-Line Decetaxel/Prednisone to Decetaxel/Prednisone in Combination with Custirsen (OGX-011) In Men With Metastatic Castrate Resistant Prostate Cancer. (OGX-11-10)	**Dr. Smith**	8	8
Totals			**21**	**20**

Task #2: We will collect and analyze blood, urine and tissue samples collected on all the consortium clinical trials that are led by the University of Michigan. (Sample Collection: Months 1-48), (Analysis: Months 48-60).
Using the consortium-developed management plan for acquisition, delivery, and storage of biological samples to the appropriate laboratories for testing or storage Sample collection for the correlative endpoints for the clinical trials are progressing, please see correlative studies column of Table 4 for a list of ongoing correlative research included in the DOD-PCCTC trials and Table 3 for a breakdown of the samples that have been collected for DOD-PCCTC trials to date.

Please see the following description of the scientific correlative objectives for two of the studies introduced to the DOD-PCCTC by the University of Michigan that highlight the scope of our efforts in this area (both trials are expected to activate at our site at the end of April or early May 2012):

1. c11-089, NCI 9012, A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer.
Correlative Objectives
    - To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and CTCs.
    - To assess if ETS fusion status in the CTCs is associated with response to therapy.
    - To evaluate changes in circulating tumor cells (CTCs) at baseline and during therapy in all patients.
    - To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
    - To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
    - To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions.
    - To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding, metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888.
    - To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.

2. c11-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer.

    Biomarkers to be assessed
    All biomarkers will be assessed in the Center for Translational Pathology at the University of Michigan Medical Center. To identify areas of cancer for further analysis all samples will undergo H&E staining with identification of regions of prostate cancer as well as classification with a Gleason score. These regions will then be assessed on parallel tissue samples for IHC analysis following construction of a tissue micro-array.

    To assess the PTEN axis the following biomarkers will be evaluated by immunohistochemical analysis

    - PTEN
    - Akt
    - Phos-Akt (Ser 473)
    - Phos-Akt (Thr 308)
    - p70S6K
    - Phos-p70S6K (Thr421/Ser424)

- 4EBP1
- Phos-4EBP1
- Stathmin

In addition, to evaluate putative markers of neo-angiogenesis and hypoxia the following additional markers will be evaluated in tumor tissue before and after everolimus therapy

- VEGF-A
- HIF1-alpha
- CD31 micro-vessel density

Table 3: Samples collected for DOD-PCCTC correlative studies to date

Correlative Studies Sample Collection		
DOD Number	Study Title	Samples Collected to date
c08-009	A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301)	97 Serum Sets
c09-031	A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease	44 Whole Blood CTC Samples 6 Whole Blood Pharmacogenetic Samples 144 Plasma Sets 22 Serum Sets
c09-033	A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	14 Skin Biopsy Samples 62 Plasma Sets 90 Whole Blood CTC samples
c09-044	A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA	30 Whole Blood CTC Samples 26 Urine Sets 51 Hematology Samples 191 Serum Sets 113 Plasma Sets
c09-057	A randomized, double-blind, placebo-controlled, multicenter Phase II trial investigating two doses of EMD 525797 in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC)	19 CTC Samples 28 PK Samples 32 Safety Samples 18 Immunogenicity Samples 25 Protein Biomarker Samples 19 Gene Expression mRNA 19 Urine Biomarker Samples 3 Pharmacogenetic assessments 1 set of 21 tumor Slides
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with theCombination of Cediranib (AZD2171) plus BMS-354825 (dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	10 Serum Sets
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	16 Sets of Archived Tumor Blocks/Slides 18 Whole Blood CTC Samples 34 Hematology Samples 29 Whole Blood Pharmacogenetic Samples 25 Serum Sets 318 Plasma Sets

Table 4. Current areas of research by stage of disease, including correlative research

Current University of Michigan DOD-PCCTC Prostate Cancer Clinical Trials Summary					
Area of Focus	**Title**	**UM PI**	**Lead Site**	**Trial Status**	**Correlative Studies**
Neoadjuvant					
Signal transduction	2011.030, c09-041, A Randomized Trial of Preoperative GDC-0449 and Androgen Ablation Alone Followed by Radical Prostectomy for Select Patients with Locally Advanced Adenocarcinoma of the Prostate (NCI 8348)	Dr. Jeffrey Montgomery	MDACC	**Administratively closed by CTEP effective 3/31/2012.**	Analyze tumor specimens for changes in hedgehog and androgen signaling, proliferation, apoptosis and markers linked to progression between the two arms; collect and archive tissue from the primary tumor, bone marrow biopsy/aspirate and blood (serum, plasma) for future studies.
Signal transduction	2011.008, c10-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer	Dr. Daniel Hamstra	**University of Michigan**	Expected to open May 2012.	To assess PTEN axis, the following biomarkers will be analyzed by IHC analysis; PTEN, Akt, Phos-Akt (Ser 473), Phos-Akt (Thr 308), p70S6K, Phos-p70S6K (Thr421/Ser424), 4EBP1, Phos-4EBP1, Stathmin; to evaluate putative markers of neo-angiogenesis and hypoxia, the following will be evaluated in tumor tissue before and after everolimus therapy; VEGF-A, HIF1-alpha, CD31 micro-vessel density.
Prostate (Rising PSA - Androgen Dependent)					
Angiogenesis/Signal Transduction	2007.086, c09-024, A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy	Dr. Maha Hussain	Chicago	**Closed permanently 4/20/2010 due to multiple early patient discontinuations**.	

Prostate (Rising PSA - Androgen Independent)					
AR signaling/Signal Transduction	2009.091, c07-044, A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA	Dr. Maha Hussain	**University of Michigan**	Closed to accrual 7/31/2011 completed accrual. .	Evaluate changes in bone turnover markers, assess archival tumor samples for candidate biomarkers including the TMRSS2/ERG fusion gene, characterize biomarkers in CTC's.
Metastatic Androgen Dependent Front Line					
Apoptosis/Signal Transduction	2008. 064 c07-012 A Phase II Study of AT101 to abrogate BCL-2 Mediated Resistance to Androgen Ablation Therapy in Patients with Newly Diagnosed Stage D2 Prostate Cancer. NCI 8014	Dr. Maha Hussain	CINJ	Met accrual goal, closed 9-14-10.	Determine changes in Bcl-2 and BAX/BAK protein expression in peripheral blood mononuclear cells and in baseline tumor tissue.
Metastatic Androgen Independent Front Line					
Angiogenesis/ (Hedgehog) Signal Transduction	2009.042, c09-033, A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	Dr. David Smith	JHU	Met accrual goal, closed 10-1-2010.	To investigate changes in itraconazole PK, serum testosterone, DHEA-S, ACTH, serum cortisol, aldosterone, and VEGF levels with time, changes in GLi1 mRNA expression levels and advanced MRI parameters with time.
Apoptosis/Signal Transduction	2010.038, c09-038, Phase II Randomized Study of Bcl-2 Inhibition with ABT-263 Combined with Androgen Ablation Therapy in Newly Diagnosed Metastatic Prostate Cancer	Dr. Maha Hussain	CINJ	**Study on hold by sponsor as of 9-24-2010. UM Site withdrew participation 4/22/2011**.	DNA samples to be analyzed for genetic factors contributing to response to in terms of PK, tolerability and safety; circulating tumor cells concentrations at screening baseline and on therapy (at baseline assessed for Bcl-2 family proteins and gene copy number).
Angiogenesis/Bone	2010.108, c09-057, A Randomized Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly	Dr. Maha Hussain	**University of Michigan**	Opened at UM site 6/9/2011.	Serum PK, mRNA levels in whole blood or tumor samples, change in circulating endothelial cell count in whole blood with clinical outcome or other drug markers.

	Asymptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)				
Signal Transduction	2010.005, c09-048, Phase I/II Trial of Anti-IGF-IR Monoclonal Antibody IMC-A12 plus mTOR Inhibitor Temsirolimus (CCI-779) in metastatic castration-resistant prostate cancer (CRPC). NCI #8417	Dr. Maha Hussain	MSKCC	**Closed 3-4-2011 by lead site (MSK) because of toxicities**.	CTC analysis, PET imaging, tumor biopsy to evaluate biomarkers.
Cytotoxic Therapy (taxane derivative)	2011.016, c10-071, A Phase II study of single-agent tesetaxel in chemotherapy-naïve and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	Dr. Maha Hussain	MSKCC	Activated at UM site on 10/21/2011.	N/A
Angiogenesis/Signal Transduction	2009.076, c11-079, A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	Dr. David Smith	**University of Michigan**	Phase II prostate cohort opened to all participating sites as of 11/18/2011.	MRI, CT scan, and/or bone scans; PK; pharmacodynamic biomarkers (eg, sMET, HGF, VEGF-A, PlGF, sVEGFR2); tumor samples assayed for signaling pathways; CTCs; genotyping /single nucleotide polymorphism analysis (pharmacogenomics); markers of bone turnover, serum NTx, CTx, and bone alkaline phosphatase
AR signaling	2011.052, c10-072, An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Advanced Castration-Resistant Prostate Cancer	Dr. David Smith	MSKCC	Activated at UM site on 12/19/2011.	Pre- and post-therapy changes in CTC number and molecular profiles in CTC.
Metastatic Androgen Independent After Docetaxol					
Signal Transduction (DNA Repair)	2009.114, c09-031, A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant	Dr. Maha Hussain	**University of Michigan**	Closed 10/22/10 met accrual goal.	Exploratory research to find biomarkers that may serve as surrogates for clinical endpoints in future ABT-888 studies or that may be predictive of ABT-888 activity will be conducted. Blood samples will be collected at designated time points throughout the study. Archivedtissue samples (if available) will be collected while subjects are on study.

	Disease				
Signal Transduction/Cytotoxic Therapy	2010.039, c09-025, Phase II trial of carboplatin and RAD001 in metastatic castrate resistant prostate cancer (CRPC) pretreated with docetaxel therapy	Dr. David Smith	Wayne State	**Novartis withdrew support on 5/18/2011. Trial terminated 6/23/2011.**	Phospho mTOR status of prostate cancer in archival tissue, PK response predictors ($p70^{s6}$/$p70^{s6}$ phosphoprotein, AKT/pAKT), PK of the 2 drugs in ~ 50% of patients.
AR signaling/Signal Transduction	2011.012, c11-089, A Randomized Gene Fusion-Stratified Phase 2 Trial Of Abiraterone With Or Without ABT888 For Patients With Metastatic Castration-Resistant Prostate Cancer: NCI 9012	Dr. Maha Hussain	**University of Michigan**	NCI activated trial on 4/18/12.	•To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and CTCs. •To assess if ETS fusion status in the CTCs is associated with response to therapy. •To evaluate changes in circulating tumor cells (CTCs) at baseline and during therapy in all patients. •To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888. •To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888. •To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions. •To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding, metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888.

					•To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.
Cytotoxic Therapy	2008.033, c08-009, A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301)	Dr. Maha Hussain	MDACC	**Closed by 2-1-11 by Celgene**.	PK samples to determine caveolin-1 levels
Angiogenesis/Signal Transduction	2011.067, c10-073, A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer: NCI 8476	Dr. David Smith	JHU (Princess Margaret Hospital)	Activated at UM site on 10/20/2011. **On-hold to accrual effective 2/14/12 due to NCI budgetary restrictions and will close by 7/31/12 due to the discontinuation of cediranib development by the sponsor**.	Bone resorption markers (e.g. c-telopeptide and bone alkaline phosphatase), and how these biomarkers correlate with clinical outcome.

Task #3: Final Analysis and Report Writing. A final clinical and statistical analysis of all data (clinical and correlative) on all University of Michigan led trials will be undertaken. A final report and draft manuscripts will be circulated to all co-authors and submitted to appropriate scientific journals for publication. (Months 54-60).

The results of the c08-001 trial (IMC-A12 and IMC-1121B) and the c09-031 trial (ABT-888) were reported by Dr. Hussain at the 2012 GU ASCO meeting (Appendix A and B). Results of the c09-044 trial (TAK-700) were reported by Dr. Hussain at the 27th EAU Congress meeting 2012 (Appendix E and F). Final reporting is awaiting mature survival data. For all other completed trials we are awaiting more mature survival and efficacy data before publishing the results. Dr. Smith is currently preparing a manuscript on the results of the c11-079 trial (XL184-Cabozantinib).

As part of their SOW, each participating site was expected to present at least 1 clinical trial each year for the consortium's consideration.

In the third year of the new DOD-PCCTC CCA research site award, the University of Michigan presented one study to the DOD-PCCTC (c11-089, ABT-888/Abi/Gene Fusion trial). The following trial was presented by University of Michigan to the consortium. This trial was accepted for consortium participation during the current reporting period (LOI was circulated 4/18/12).

c11-089 - **A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer.** This study is an investigator initiated CTEP sponsored biomarker stratified and randomized phase II trial that will evaluate the role of ETS gene fusion as a predictive biomarker for response to hormone therapy alone or hormone therapy plus PARP-1 targeted therapy in patients with mCRPC. The study will also evaluate whether the addition of PARP-1 targeted therapy is superior to hormone therapy based on gene fusion status. The scientific rationale for this study is supported by:

1. Abiraterone is FDA approved based on prolonging survival in patients with mCRPC post docetaxel; however the effect is modest and not all patients benefit.
2. ETS gene fusions are predominantly driven by an androgen-sensitive promoter. Data from radical prostatectomy series suggest that ETS fusion status predicts for response to adjuvant androgen deprivation therapy[1]and preliminary data from phase I/II studies of mCRPC patients suggest that abiraterone may have greater therapeutic effect in ETS-fusion positive prostate cancer patients. [2,3]
3. There is interaction of PARP1 with the androgen signaling cascade, regardless of ETS fusion status and with ETS fusions; our data indicate that ERG-positive xenografts are preferentially sensitive to PARP-1 inhibitors.
4. ABT-888 has been demonstrated to have efficacy across a wide range of tumor types in preclinical studies.[4] ABT-888 has been demonstrated to inhibit PARP1 in a clinical phase 0 study, and is currently being assessed as a component of combination therapy across a range of tumor types clinically, including breast, liver, and ovarian cancer, as well as an unselected metastatic prostate cancer population. We have conducted in collaboration with Abbott and the DOD-PCCTC, a clinical trial with ABT-888: M11-070 Protocol, A Phase II Study Combining ABT-888 (an Oral PARP Inhibitor) + Temozolomide in Patients with Metastatic Castration Resistant Prostate Cancer Who Have Failed Up to Two Non-hormonal Systemic Therapies (c09-031). The interim data suggests it's feasible to administer ABT-888 in combination and that there is a signal of clinical activity.

OBJECTIVES

- Primary Objectives
  - To evaluate the role of ETS gene fusion as a predictive biomarker for response to hormone therapy (abiraterone) alone or hormone therapy plus PARP-1 targeted therapy (ABT-888) in patients with metastatic castration resistant prostate cancer.
  - To evaluate whether the addition of PARP-1 targeted therapy is superior to hormone therapy alone based on ETS gene fusion status.
- Secondary Objectives

- Rate of PSA declines.
- Objective response rate.
- Progression-free survival.
- Evaluate the qualitative and quantitative toxicity of abiraterone acetate with and without ABT-888.

o Correlative Objectives
- To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and CTCs.
- To assess if ETS fusion status in the CTCs is associated with response to therapy.
- To evaluate changes in circulating tumor cells (CTCs) at baseline and during therapy in all patients.
- To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions.
- To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding, metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888.
- To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.

The University of Michigan is the lead site, with the University of Chicago acting as the coordinating center for this multicenter study. Ten sites in the US will participate in the trial. In addition, two additional sites are interested in joining. 148 subjects will be randomized. This trial will be conducted as part of the University of Chicago Phase II Consortium sponsored by CTEP and through the Department of Defense (DOD) Prostate Cancer Clinical Trials Consortium (DOD-PCCTC). Six other DOD-PCCTC member sites have confirmed they will participate in this study (Johns Hopkins University, MD Anderson Cancer Center, University of Wisconsin, Cancer Institute of New Jersey, University of Washington, and the University of Chicago). CTEP approved and activated this study on 3/30/2012 and our site was activated on 4/18/2012. This trial is one of the lead trials selected to be part of the Stand Up to Cancer (SU2C) – Prostate Cancer Dream Team Translational Cancer Research Grant (AACR/PCF).

DOD-PCCTC participating institutions are charged with maintaining an annual accrual rate of 35 patients to DOD-PCCTC participating trials.

Currently, there are five DOD-PCCTC trials actively accruing (c09-057, EMD 525797), (c10-071, Tesetaxel), (c11-079, XL184), (c10-072, ARN-509) and (c11-089, ABT-888/Abi/Gene fusion), one trial pending site activation (c11-080, Everolimus), and one trial recently closed to accrual (c09-044 TAK-700). The University of Michigan has accrued 20 patients during the third year of this award year award period, despite the early closure and termination of 4 trials during this reporting period (c09-041, GDC-0449, activated 2/28/12, CTEP administratively closed 3/16/12), (c09-038-ABT-263, study on indefinite hold 9/24/10, UM site withdrew 4/22/11), (c09-025,Carbo/RAD001, study activated 5/9/11, sponsor withdrew support 5/18/11, trial terminated 6/10/11), and (c10-073, Cediranib/Dasatinib, activated 10/21/11, NCI on-hold to accrual 2/14/12, study to close by 7/31/12) in most cases, right after we had just activated the trials. We are confident once these new trials open we will be able to maintain an annual accrual rate of 35 patients to DOD-PCCTC participating trials. **Please refer to Table 4 for trial status information and Table 2 for the accrual numbers for the trials that accrued in this period.**

University of Michigan **Biomarker Trials**

Currently we are participating in two DOD-PCCTC biomarker trials, b11-011, SWOG S0925, A Randomized Phase II Study of Combined Androgen Deprivation Versus Combined Androgen Deprivation with IMC-A12 for Patients with New Hormone Sensitive Metastatic Prostate Cancer (SWOG 0925) and b11-010, A Randomized Phase 3 Study Comparing Standard First-Line Decetaxel/Prednisone to Decetaxel/Prednisone in Combination with Custirsen (OGX-011) In Men With Metastatic Castrate Resistant Prostate Cancer. (OGX-11-10) Phase III study of Docetaxel and Atrasentan versus Docetaxel and placebo for patients with advanced hormone refractory prostate cancer. During this reporting period, we accrued twelve patients to the SWOG S0925 study (13 total at our site) and eight patients (8 total at our site) to the OGX-011 study **(see Table 2)**.

KEY ACCOMPLISHMENTS

University of Michigan Comprehensive Cancer Center

As of March 31, 2012, our accomplishments during the award period are listed below.

Infastructure

• Collaborated with other DOD-PCCTC sites to improve the data collection process with the consortium database, to make the system more time effective and accurate.

• Participated in all the Prostate Cancer Clinical Trials Consortium meetings, including the most recent PCCTC PI Investigators meeting on December 8th and the DOD-EAB review meeting held December 9th, 2011 in Fair Lakes, Virginia.

• Extended collaboration between the DOD-PCCTC and the University of Chicago CTEP-sponsored Phase II Consortium and other non-consortium sites.

Research/Protocol Development

•Introduced six trials to date to the DOD-PCCTC consortium for the first three years of the new award period (effective April 1, 2009) (see also **Table A. Trials Introduced by the University of Michigan**)

1. c09-031, ABT-888 – LOI circulated 2/25/2009
2. c09-044, TAK-700 – LOI circulated 7/9/2009
3. c09-057, EMD 525797 – LOI circulated 12/11/09 and 4/28/10
4. c11-079, XL184 – LOI circulated 1/5/11
5. c11-080, Everolimus – LOI circulated 2/10/11
6. c11-089, ABT-888/Abi/Gene Fusion – LOI circulated 8/10/11

• Served as the lead site for the DOD-PCCTC for five protocols to date for the first three years of the new award period (effective April 1, 2009).

1. c09-031, ABT-888 – UM site activated 5/17/10
2. c09-044, TAK-700 – UM site activated 4/8/10
3. c09-057, EMD 525797 – UM site activated 6/9/11
4. c11-079, XL184 – UM site activated 12/7/09 (to DOD-PCCTC 1/5/11)
5. c11-089, ABT-888/Abi/Gene Fusion – UM site activated 4/18/12

•Will serve as the lead site for one other trial (anticipate activation in May 2012).

1. c11-080, Everolimus

•Completed the seven protocols to date for the first three years of the new award period (effective April 1, 2009). Two of these protocols completed during this reporting period (April 1, 2011 to March 31, 2012).

1. c07-012, AT-101- closed 9/14/10
2. c08-009, Nab-docetaxel – closed 10/20/09 – re-opened 12/10/10 – closed 1/31/11
3. c09-024, Pazopanib- closed 4/20/10
4. c09-031, ABT-888 – closed 10/22/10
5. c09-033, Itraconazole – closed 10/1/10
6. c09-044, TAK-700 – closed 6/17/11
7. c10-072, Cediranib/Dasatinib – on-hold to accrual 2/14/12, to close by 7/31/12.

•Three of the DOD-PCCTC trials that were active, or soon to be activated, during for the first three years of the new award period were based on scientific data generated by our group.

1. c07-012, AT-101, trial was based on an agent that was developed by a University of Michigan scientist through work funded by our Prostate Cancer SPORE. The study design of the protocol was based on data published by Dr. Hussain regarding the relationship of PSA nadir after ADT with survival in new M1 patients. The trial completed accrual in 18 months and closed in September 2010.
2. c11-080, Everolimus, Dr. Daniel Hamstra wrote the protocol for this study, which was based on pre-clinical work supported by a Young Investigator Award from the PCF. Trial is expected to activate in May 2012.

3. c11-089, ABT-888/Abi/Gene Fusion- The TMPRSS2-ETS gene fusion was discovered by a University of Michigan researcher. Trial was activated on 4/18/2012.

• Accrued 91 patients to DOD-PCCTC trials to date for the first three years of the new award period (105 in the previous three year award period).
• Collected 1,504 samples for correlative studies of DOD-PCCTC trials at the end of the third year of the award period (with ~1,500 samples from the previous three year award period).

REPORTABLE OUTCOMES

University of Michigan Comprehensive Cancer Center

During the 3nd year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 4 abstracts (c08-001, IMC A-12, IMC-1121B), (c09-031, ABT-888) (c09-033, Itraconazole) and (c09-044, TAK-700; 3 poster presentations (c08-001, c09-031 and c09-044); 1 oral presentation (c09-044), and 1 manuscript (c09-024). The abstract and all manuscripts have been published. A complete listing of abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section. In this reporting period, during our third 12 months of funding, two studies were closed (c09-044, TAK-700 on 6/17/11) having met the accrual goal and (c010-073, Cedirinib/Dasatinib) (on-hold to accrual as of 2/14/12, study to close by 7/31/12). Dr. Hussain was a co-author on the c09-024 (Pazopanib) manuscript in the journal Prostate Cancer and Prostatic Diseases (see **Appendix G**).

During this reporting period, the following abstracts/posters were presented at the following scientific meetings:

c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC 1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 97). Author: Dr. Maha Hussain. **(Appendix A)**

c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224). Author: Dr. Maha Hussain. **(Appendix B)**

c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial. American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). Co-author: Dr. David C. Smith. **(Appendix C)**

c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516). Author: Dr. Maha Hussain. Co-author: David C. Smith. **(Appendix D)**

c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study. Abstract and poster presented by Dr. Hussain at the 27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012. **(Appendix E and F)**

CONCLUSIONS

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan during this reporting period (04-01-2011 to 03-31-2012) of the DOD-PCCTC CCA research site award are summarized in this report.

The focus of the University of Michigan during the this period of the DOD-PCCTC has been to work with consortium investigators and outside sponsors to bring novel research to the DOD-PCCTC, to actively accrue to DOD PCCTC trials, and to expand collaboration with other non-consortium institutions.

University of Michigan research personnel have actively participated in a variety of activities to facilitate research and communication between participating institutions including teleconferences, scheduled conference calls and Investigator meetings.

The University of Michigan has presented a total of six studies to the DOD-PCCTC for member participation since April 2009 (see study list in Key Accomplishments section, Research/Protocol Development).

Currently, there are five DOD-PCCTC trials actively accruing at the University of Michigan (c09-057, EMD 525797), (c10-071, Tesetaxel), (c10-072, ARN-509), (c10-073, Cedirinib/Dasatinib), (c11-079 XL184), and (c11-089, ABT-888/Abi/Gene fusion) with one additional study (c11-080, Everolimus) that will be activated in May 2012

We have accrued 91 patients to DOD-PCCTC trials to date at the end of this third year of the new award (20 during this reporting period, with 5% accrued from disproportionately affected populations).

We have activated four new consortium trials during this reporting period.

1. c09-057, EMD 525797 – activated 6/9/11
2. c10-071, Tesetaxel – activated 10/21/10
3. c10-073, Cedirinib/Dasatinib – activated 10/20/11
4. c11-089, ABT-888/Abi/Gene Fusion – activated 4/18/12

Our efforts have led to several national presentations and publications.

In addition to improving therapy our trials have a variety of embedded correlatives aimed at better understanding mechanisms of response and progression.

To date, we have collected approximately 1,504 samples (with ~1,500 samples from the previous three year award period) for the correlative endpoints to DOD-PCCTC trials.

In the 3rd year of this new funding period with the DOD-PCCTC, the University of Michigan will continue accrual to active consortium trials, will introduce new concepts that will capitalize on the scientific productivity of our group coupled with the accrual and scientific strength of the DOD-PCCTC, open additional consortium trials and continue to finalize analysis and reporting of completed projects

REFERENCES

1. Karnes RJ, Cheville JC, Ida CM, et al: The ability of biomarkers to predict systemic progression in men with high-risk prostate cancer treated surgically is dependent on ERG status. Cancer Res 70:8994-9002, 2010
2. Attard G, Reid AH, Yap TA, et al: Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 26:4563-71, 2008
3. Attard G, Swennenhuis JF, Olmos D, et al: Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer Res 69:2912-8, 2009
4. Palma JP, Wang YC, Rodriguez LE, et al: ABT-888 confers broad in vivo activity in combination with temozolomide in diverse tumors. Clin Cancer Res 15:7277-90, 2009

Appendices
University of Michigan Comprehensive Cancer Center

Abstracts:

1. c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. **Maha Hussain**, Dana Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna Ferrari, John Hainsworth, Ling Yang, Jonathan Schwartz, Hagop Youssoufian, Celestia S. Higano. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 97). **(Appendix A)**

2. c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). **Maha Hussain**, Michael Anthony Carducci, Susan F. Slovin, Jeremy Paul Cetnar, Jiang Qian, Evelyn Mary McKeegan, Elizabeth Litvinovich, Brenda Chyla, Robert Hetman, Bhardwaj Desai, Vincent L. Giranda, Joshi J. Alumkal. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224). **(Appendix B)**

3. c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial. . S. Antonarakis, E. I. Heath, **D. C. Smith**, D. E. Rathkopf, A. L. Blackford, D. C. Danila, S. King, A. Frost, M. A. Carducci. American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). UMICH - co-author. **(Appendix C)**

4. c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. **M. Hussain**, M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara, C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, **D. C Smith**. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516). **(Appendix D)**

5. c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study. **Hussain, M.**, Corn, P., Michaelson, D., Hammers, H., Alumkal, J., Ryan, C., Bruce, J., Moran, S., Mortimer, P., Lee, S.Y., George, D. Abstract and poster presented by Dr. Hussain at the 27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012 (abstract and poster #124). **(Appendix E and F)**

Manuscripts:

1. c09-024 - A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study. JE Ward, T Karrison, G Chatta, **M Hussain**, D Shevrin, RZ Szmulewitz, PH O'Donnell, WM Stadler and EM Posadas. Prostate Cancer and Prostatic Diseases (2012) 15, 87–92. **PMID 22006050** [PubMed – in process] **(Appendix G)**

SUPPORTING DATA
University of Michigan

Table A. Trials Introduced by the *University of Michigan* (as of 04/01/2011)

LOI #	Protocol Title (Phase, Intervention, Population)	Target Accrual	Current Accrual (UM/ Other Sites)	Submitted		PI	PCCTC-DOD Participating Sites	Outcomes
				Start Date	End Date			
c09-031	A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease	25	26(6/20)	5/17/2010	10/22/10	Dr. Maha Hussain	MSK, OHSU, UCSF, UWisc	Met accrual goal.
c09-044	A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA	42	33(6/27)	4/8/2010	6/17/11	Dr. Maha Hussain	DF-HCC, OHSU, JHU, UCSF, MDACC, UWisc, Duke	Met accrual goal.
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	225	30(4/26)	6/09/2011	Open and accruing	Dr. Maha Hussain	MDACC, CINJ, Wayne State, UChicago	
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	370	86(30/56)	12/17/09 1/5/11 to PCCTC	Open and accruing	Dr. David Smith	MSK, DF-HCC, UCSF, MDACC, Wash, Duke, Wayne State	
c11-080	A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High	40		Expected to open May 2012		Dr. Daniel Hamstra	JHU, UChicago (NWestern)	

	Risk Prostate Cancer							
c11-089	A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer	148		4/18/2102		Dr. Maha Hussain	JHU, MDACC, CINJ, Wayne State, UChicago, Wash	

Table B. Trials in Which the *University of Michigan* Participated (as of 04/01/2011)

LOI #	Protocol Title (Phase, Intervention, Population)	Target Accrual	Current Accrual (UM/Other Sites)	Submitted		University of Michigan PI	Lead Site	Other Participating Sites
				Start Date	End Date			
c09-044	A Phase 2 Multicenter Open-label Study Evaluating the Safety and Efficacy of TAK-700 in Patients with Nonmetastatic Castration-resistant Prostate Cancer (CRPC) and a Rising Prostate-specific Antigen (PSA)	42	33(6/27)	4/8/2010	6/17/11	Dr. Maha Hussain	UMICH	DF-HCC, OHSU, JHU, UCSF, MDACC, UWisc, Duke
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	225	30(4/26)	6/09/2011	Open and accruing	Dr. Maha Hussain	UMICH	MDACC, CINJ, Wayne State, UChicago
c10-071	A Phase II study of single-agent tesetaxel in chemotherapy-naive and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	57	14(4/10)	10/21/2011	Open and accruing	Dr. Maha Hussain	MSKCC	UCSF, UWisc, CINJ
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	370	78(29/56)	12/17/09 1/5/11 open to PCCTC	Open and accruing	Dr. David Smith	UMICH	MSKCC, DF-CI, UCSF, MDACC, Wash, Duke, Wayne State
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	50	10(3/7)	10/20/2011	On hold to accrual as of 2/14/2012; closing by 7/31/12	Dr. David Smith	JHU	

c10-072	An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Advanced Castration-Resistant Prostate Cancer	132	58(1/57)	12/19/2011	Open and accruing	Dr.David Smith	MSKCC	OHSU, JHU, UWisc, Wash

Table C. Quarterly Patient Accrual by the *University of Michigan* (as of 04/01/2011)

Quarter	Accrual Per Quarter	DAP Accrual Per Quarter	Total Accrual To Date
2Q11	3		3
3Q11	2		5
4Q11	7		12
1Q12	7	1	20

Table D. *University of Michigan* disproportionately affected populations (DAP) accruals by individual trials and accrual totals (as of 04/01/2011)

DOD#	White	African-American	White Hispanic	Total
c09-044	**1**			**1**
c09-057	**4**			**5**
c10-071	**5**			**10**
c10-073	**3**			**13**
c11-079	**6**	**1**		**20**
Total	**19** **95%**	**1** **5%**		**100%**

Table E. The *University of Michigan* patient contribution to other DOD-PCCTC member trials (as of 04/01/2011)

UMich site led studies (Accrual #)			UMich site accruals to other consortium site led studies (Accrual #)	
c11-079 XL184	(7)		c10-071 Tesetaxel	(5)
c09-044 TAK700	(1)	c10-073	Ced/Dasatinib	(3)
c09-057 EMD525797	(4)			
Total	12			8
% total of accruals	**60**			**40%**

Table F. Personnel Receiving Pay From the Research Effort at the *University of Michigan*

Role	**Name**
Principal Investigator	Maha Hussain, MD
Co-Investigator	David C. Smith, MD
Co-Investigator	Kenneth J. Pienta, MD
Co-Investigator	Kathleen Cooney, MD
Co-Investigator	Ajjai Alva, MD
Clinical Research Coordinator-Reg	Charles Leister
Clinical Research Administrator	Gregory Campbell
Research Nurse	Tamara Huebner
Research Nurse	Heidi Robb
GU Data Manager	Patricia Jo Harvey
GU Data Manager	Amie Anderson
Biostatistician	Stephanie Daignault-Newton

Appendix A

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A phase II randomized study of cixutumumab (IMC-A12: CIX) or ramucirumab (IMC-1121B: RAM) plus mitoxantrone (M) and prednisone (P) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following disease progression (PD) on docetaxel (DCT) therapy.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2012 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session B: Prostate Cancer
Abstract No:
97
Citation:
J Clin Oncol 30, 2012 (suppl 5; abstr 97)
Author(s):
Maha Hussain, Dana E. Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna C. Ferrari, John D. Hainsworth, Ling Yang, Jonathan D. Schwartz, Celestia S. Higano; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; University of Wisconsin Carbone Cancer Center, Madison, WI; Duke Cancer Institute, Durham, NC; Thomas Jefferson University Hospital, Philadelphia, PA; New York University Cancer Institute, New York, NY; Sarah Cannon Research Institute, Nashville, TN; ImClone Systems, Bridgewater, NJ; Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract Disclosures

Abstract:

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis and insulin-like growth factor (IGF-IR)-mediated signaling contribute to mCRPC growth. CIX and RAM are fully human IgG1 human monoclonal antibodies targeting IGF-IR and VEGF receptor-2 (VEGFR-2) respectively. We investigated the safety and efficacy of CIX or RAM in combination with M + P in mCRPC pts with PD on DCT. **Methods:** Eligible pts had mCRPC and PD during/within 120 days of DCT, ECOG PS 0-2, PSA ≥ 2 ng/mL, and adequate organ function. All pts received M 12 mg/m^2 IV every 3 weeks (w) + P 5 mg PO BID for up to 12 cycles and were randomized to either CIX 6 mg/kg or RAM 6 mg/kg IV q w. Tumor assessments were after the first 3 cycles and then q6w. Primary endpoint was composite progression-free survival (cPFS: either RECIST PD, bone scan PD or new skeletal events). Other endpoints included safety, response and overall survival (OS). Sample size was based on a targeted 50% increase in median (mdn) cPFS from 2.6 months (m) to 3.9 m. **Results:** 132 pts were treated; 66 each to CIX or RAM. Mdn age and baseline PSA was 65 yr and 129 ng/mL for pts treated with CIX and 68 yr and 111 ng/mL for RAM. Involvement of sites other than bone was CIX: 79% and RAM: 70%. The most frequent Grade ≥3 related adverse events for CIX/M/P: fatigue 17%, leukopenia 12%, and neutropenia 8%, and for RAM/M/P: leukopenia 8%, neutropenia 8% and hypertension 8%. Left ventricular dysfunction/CHF: 12% for CIX (0% G3) and 23% for RAM (8% G3). Mdn number of Rx cycles were 5 for CIX and 6 for RAM. Mdn follow-up was 22.7 m for CIX and 21.8 m for RAM. PSA response was 18.4% (8.8-32% 95% CI) on CIX and 22.0% (11.5-36% 95% CI) on RAM. Mdn cPFS and OS were 4.1 m (3.0-5.6 m 95% CI) and 10.8 m (6.5-13.0 m 95% CI) for CIX and 6.7 m (4.5-8.3 m 95% CI) and 13.0 m (9.5-16.0 m 95% CI) for RAM. **Conclusions:** CIX/M/P and RAM/M/P were reasonably tolerated and achieved the primary endpoint. Preliminary cPFS and OS of RAM/M/P appear encouraging; sustained disease control was observed in pts on both rx arms. Correlation of serum markers of IGF and VEGF activity with clinical endpoints is planned.

Appendix B

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Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2012 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session C: Prostate Cancer
Abstract No:
224
Citation:
J Clin Oncol 30, 2012 (suppl 5; abstr 224)
Author(s):
Maha Hussain, Michael Anthony Carducci, Susan F. Slovin, Jeremy Paul Cetnar, Jiang Qian, Evelyn Mary McKeegan, Elizabeth Litvinovich, Brenda Chyla, Robert Hetman, Bhardwaj Desai, Vincent L. Giranda, Joshi J. Alumkal; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; University of Wisconsin, Madison, WI; Abbott Laboratories, Abbott Park, IL; Oregon Health and Science University, Portland, OR

Abstract Disclosures

Abstract:

Background: Castration-resistant PC tumors exhibit increased PARP activity (critical enzymes for DNA damage repair). Veliparib is a novel, oral, potent inhibitor of PARP-1 and PARP-2. Preclinically, resistance to oral TMZ treatment in the PC3-Luc prostate cancer mouse model was reversed when mice were treated with veliparib. Based on the synergistic interaction, we evaluated the efficacy and safety of veliparib + TMZ in mCRPC pts. **Methods:** Eligible pts had mCRPC, PSA>2 ng/mL, progressed on at least one docetaxel based therapy and adequate organ function. Pts received veliparib 40 mg BID Days (D) 1-7 and TMZ D1-5 in 28D cycle (C) until disease progression (PD) or unacceptable toxicities. Tumor response was assessed every 8 weeks. Primary objective: Efficacy based on rate of PSA decline of 30% or greater. Secondary objectives: safety, RECIST objective response rate, progression-free survival (PFS), overall survival (OS) and biomarker analyses. A sample size of 25 pts provided 76% power to differentiate between PSA response rates of 5 and 20% at 1-sided type I error rate of 0.1. **Results:** 26 pts were enrolled; median age 67 years [55, 81]; median baseline PSA 107 ng/ml (6.9, 4584.4); 7/26 (27%) had 2 prior therapies. Median Cs of veliparib + TMZ received were 2 (range 1-9). Most frequent treatment related adverse events (AE) were fatigue (50%), nausea (38%) and constipation (23%). Grade 3/4 AEs in >10% of pts was thrombocytopenia (15%). All pts are off therapy. 25 pts were PSA response evaluable; 2 pts had a confirmed PSA response; 1 pt had a 37% decrease in PSA while the other pt had a 96% decrease in PSA and a 40% reduction in tumor size. 4/25 pts had stable disease for a minimum of 4 months (m). Median PFS was 2.1 m [95% CI: 1.8, 3.9]; 11/26 pts have died with median OS of 9.1 m [95% CI: 5.5, 11.7]. There was a negative correlation between change from baseline in circulating tumor cells and PFS. **Conclusions:** Veliparib + TMZ were well tolerated with evidence of some activity. Due to lack of activity of TMZ in CRPC,veliparib-induced potentiation of TMZ may not be clinically significant. Other combinations will be explored with higher doses of veliparib. Biomarker data will be presented.

Appendix C

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A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 ASCO Annual Meeting
Session Type and Session Title:
Poster Discussion Session, Genitourinary (Prostate) Cancer
Abstract No:
4532
Citation:
J Clin Oncol 29: 2011 (suppl; abstr 4532)
Author(s):
E. S. Antonarakis, E. I. Heath, D. C. Smith, D. E. Rathkopf, A. L. Blackford, D. C. Danila, S. King, A. Frost, M. A. Carducci, Prostate Cancer Clinical Trials Consortium (PCCTC); The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Karmanos Cancer Institute, Detroit, MI; University of Michigan, Ann Arbor, MI; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; The Johns Hopkins University School of Medicine, Baltimore, MD; Memorial Sloan-Kettering Cancer Center, New York, NY; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Abstract Disclosures

Abstract:

Background: The antifungal drug itraconazole inhibits angiogenesis and Hedgehog signaling, and delays tumor growth in murine prostate cancer xenograft models. Unlike ketoconazole, it does not suppress adrenal androgen synthesis. **Methods:** A phase II study of oral itraconazole in men with chemo-naïve mCRPC (30% ketoconazole-pretreated) was conducted in 4 PCCTC sites. Men were randomized to low dose (LD) or high dose (HD) itraconazole (200 or 600 mg/d) until disease progression or unacceptable toxicity. The primary endpoint was PSA progression-free survival (PPFS) at 24 wk (PSA progression = 25% PSA rise above baseline/nadir; PCWG2 criteria); a 45% success rate in either arm was prespecified as constituting clinical significance. Secondary endpoints were progression-free survival (PFS) at 24 wk (progression = clinical/radiographic progression or death, but not rising PSA; PCWG2 criteria); median PFS; median PPFS; and max PSA decline. Exploratory outcomes were CTC enumeration, and analysis of serum testosterone (T) and DHEA-S. **Results:** The HD arm enrolled to completion (N=29), but the LD arm closed early (N=17) due to a prespecified futility analysis. After a median follow-up of 21.6 wk (HD arm) and 11.9 wk (LD arm), 24/29 and 17/17 men were evaluable for the primary endpoint. Efficacy results are shown below. In addition, 3/5 men (60%) in the HD arm and 2/3 men (67%) in the LD arm with unfavorable (≥5) CTCs at baseline converted to favorable (<5) CTC counts with treatment. Itraconazole did not reduce serum T or DHEA-S levels. Common toxicities (≥20%) were fatigue, nausea, anorexia, rash, and hypokalemia/hypertension/edema. **Conclusions:** Only the HD arm met its primary endpoint. Itraconazole 600 mg/d has single-agent activity in men with mCRPC that is not mediated by androgen suppression, and warrants further study.

Endpoint	Dose	Value	95% CI
Primary			
PPFS at 24 wk (%)	LD	11.8	3.2-43.2
	HD	48.4	32.1-73.0
Secondary			
PFS at 24 wk (%)	LD	18.8	6.8-52.0
	HD	61.1	44.1-84.6
Median PFS (wk)	LD	11.9	11.9-29.1
	HD	35.9	13.0-60+
Median PPFS (wk)	LD	11.9	5.6-20.0
	HD	17.0	12.4-29.0
≥30% PSA decline (%)	LD	5.9	0.2-28.7
	HD	28.6	13.2-48.7
≥50% PSA decline (%)	LD	0	0-19.5
	HD	14.3	4.0-32.7

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Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 ASCO Annual Meeting
Session Type and Session Title:
Oral Abstract Session, Genitourinary Cancer (Prostate)
Abstract No:
4516
Citation:
J Clin Oncol 29: 2011 (suppl; abstr 4516)
Author(s):
M. Hussain, M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara, C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, D. C. Smith; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Pinnacle Oncology Hematology, Scottsdale, AZ; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of California, San Francisco, San Francisco, CA; University of California, Davis, Sacramento, CA; National Taiwan University Hospital, Taipei, Taiwan; Assaf Harofeh Medical Center, Zerifin, Israel; US Oncology Research, LLC, The Woodlands, TX; Virginia Cancer Specialists, PC, Fairfax, VA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Exelixis, South San Francisco, CA; University of Michigan Cancer Center, Ann Arbor, MI

Abstract Disclosures

Abstract:

Background: Cabozantinib (Cabo) is an inhibitor of MET and VEGFR2. MET signaling promotes tumor growth, invasion and metastasis. **Methods:** mCRPC patients (pts) with progressive measurable disease (mRECIST) received Cabo at 100 mg qd PO over a 12 week (wk) lead-in stage. Response was assessed q6 wks. Treatment ≥ wk 12 was based on response: pts with PR continued open-label Cabo, pts with SD were randomized to Cabo vs placebo, and pts with PD discontinued. Primary endpoint was objective response rate (ORR) per mRECIST in the lead-in stage. Up to 200 pts could be enrolled to target 70 randomizations. Bone scans (b-scans) were independently reviewed. **Results:** Accrual was halted at 168 pts based on an observed high rate of clinical activity. 100 pts are currently evaluable for the lead-in stage; median age 68, 47% with visceral disease, 78% with bone metastasis, and 47% docetaxel (D) pretreated. Median f/u was 4 months (range, 1-15); median PFS not yet reached. Most common related Grade 3/4 AEs were fatigue (11%), HTN (7%), and hand-foot syndrome (5%); no related Grade 5 AEs reported. Dose reductions for AEs occurred in 51% of pts, and discontinuations in 10%. Bone effects: 86% (56/65 pts evaluable by b-scan) had complete or partial resolution of lesions on b-scan as early as wk 6. Eight pts (12%) had SD and 1 pt (2%) had PD. In 28 pts receiving narcotics for bone pain, 64% had improved pain and 46% decreased or halted narcotics, per investigator. Median maximum rise in hemoglobin in anemic pts (Hb < 11 g/dL) was 2.2 g/dL (range, 0.6-3.5). Osteoclast and osteoblast effects were observed: 55% had declines of ≥50% in plasma C-Telopeptide; 56% of pts with elevated tALP had declines of ≥50%. Soft tissue effects: Objective tumor shrinkage occurred in 84% of pts. ORR at wk 12 was 5%; 3 additional PRs await confirmation. PSA changes were independent of clinical activity. Overall, wk 12 disease control rate (PR+SD) was 71%. Randomization was halted and pts unblinded due to high rates of b-scan resolution and pain relief. **Conclusions:** Cabo showed clinical activity regardless of prior D in mCPRC pts, particularly in pts with bone disease, as reflected by high rates of b-scan resolution and pain relief, in addition to improvements in Hb and tumor regression.

APPENDIX E
Abstract #124

This abstract was presented during the past27th Annual Congress of the European Association of Urology	
Type:	**Poster Session**
Session:	**Treatment of advanced prostate cancer**
Date:	**Saturday February 25, 2012 from 14:15 to 15:45**
Room:	**Room Concorde Centre - Level 4**

Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study

Hussain, M.[1], Corn, P.[2], Michaelson, D.[3], Hammers, H.[4], Alumkal, J.[5], Ryan, C.[6], Bruce, J.[7], Moran, S.[8], Mortimer, P.[9], Lee, S.Y.[10], George, D.[11]

[1]University of Michigan Comprehensive Cancer Center, Dept of Internal Medicine, Ann Arbor, United States of America, [2]MD Anderson Cancer Center, Dept. of Genitourinary Medical Oncology, Houston, United States of America, [3]Massachusetts General Hospital Cancer Center, Dept. of Genitourinary Cancer, Boston, United States of America, [4]Sidney Kimmel Comprehensive Cancer Center, Dept. of Oncology, Baltimore, United States of America, [5]Oregon Health & Science University, Dept. of Internal Medicine, Portland, United States of America, [6]UCSF Helen Diller Family Comprehensive Cancer Center, Dept. of Medicine, San Francisco, United States of America, [7]University of Wisconsin Carbone Cancer Center, Dept. of Medicine, Madison, United States of America, [8]Millennium Pharmaceuticals, Inc, Dept. of Oncology Clinical Research, Cambridge, United States of America, [9]Takeda Global Research & Development Centre (Europe) Ltd., Dept. of Clinical Science, London, United Kingdom, [10]Millennium Pharmaceuticals, Inc, Dept. of Biostatistics, Cambridge, United States of America, [11]Duke University Medical Center, Dept. of Medicine, Durham, United States of America

Introduction & Objectives

Androgen signaling continues to be important in CRPC. Ortl is an investigational, oral, non-steroidal, selective 17,20-lyase inhibitor that suppresses androgen production and is in development for CRPC. Ortl has limited inhibition of 17α-hydroxylase, and may have less effect on cortisol synthesis, allowing steroid-free dosing. We evaluated ortl 300mg BID in men with nonmetastatic CRPC and rising PSA (NCT01046916).

Material & Methods

Eligible men had baseline PSA ≥2ng/mL + doubling time ≤8 mo or PSA ≥8ng/mL + doubling time >8 mo, and surgical or ongoing medical castration, with testosterone <50ng/dL. Prior chemotherapy, aminoglutethimide or ketoconazole, or concomitant corticosteroids were excluded. Starting dose was 300mg BID given continuously in 28-d cycles, optionally increasing to 400mg BID if ≥50% decrease in PSA (PSA50) was not achieved after 3 mo. Ortl was continued until PSA progression or metastases. The primary endpoint is the percentage of men with PSA ≤0.2ng/mL after 3 mo. 38 patients will provide 90% power for 1-sided significance level of 0.1 (H_0 5% vs. H_A 20%). Other endpoints include safety, 3 and 6 mo PSA30, PSA50, PSA90 rates, progression-free survival, time to PSA progression, time to metastases, changes in endocrine markers and circulating tumor cell (CTCs).

Results

38 men with a median age 71 y (range 55-81), ECOG PS 0/1 (84%/16%), median PSA 12.5ng/mL (2.6-67.8), testosterone 0.267nmol/L (0.05-0.60), and ACTH 19.5ng/L (n=32; 0-47) were treated. Median number of cycles was 5.5 (1-13); 1 patient had dose reduction due to adverse events (AEs), 1 had dose increase to 400mg BID. 99% of the total planned dose was taken. Gr ≥3 AEs occurred in 16 men (drug-related in 13); most common (≥5%) were dyspnea (11%), hypertension (8%), fatigue, hypokalemia, pneumonitis (5% ea). Seven men (18%) had serious AEs; most common was pneumonitis (2=Gr3, 1=Gr2). Eight men discontinued ortl due to AEs (dyspnea, pneumonitis, adrenal insufficiency, fatigue, hypertension, diarrhea, dysgeusia). At 3 mo, 4 men (11%) achieved PSA ≤0.2ng/mL. PSA50 and PSA90 rates were 69% and 28%, respectively. At 3 mo, median PSA decline was 83% to 1.96ng/mL (n=28; 0.12-50.5); median testosterone declined by 89% to 0.026nmol/L (0-0.28), and median ACTH increased by 228% to 55ng/L (12-351). Similar results were seen at 6 mo, with changes of –87% to 2.05ng/mL (0.1-12.3), –86% to 0.033nmol/L (0.01-0.41), and +312% to 83.5ng/L (21-173), respectively. 6-mo PSA50 and PSA90 rates were 42% and 17%, respectively. 14 men (37%) were on treatment >6 mo. Of 35 men with baseline CTC/7.5mL values, only 1 had CTC ≥5 and 6 had 1-4 CTC.

Conclusions

Ortl given without steroids is feasible in men with nonmetastatic CRPC, has manageable toxicities, and produces substantial and durable declines in testosterone and PSA.

Poster 124

Activity and Safety of the Investigational Agent Orteronel in Men With Nonmetastatic Castration-resistant Prostate Cancer and Rising Prostate-specific Antigen: Results of a Phase 2 Study

Maha Hussain,[1] Paul Corn,[2] Dror Michaelson,[3] Hans Hammers,[4] Joshi Alumkal,[5] Charles Ryan,[6] Justine Bruce,[7] Susan Moran,[8] Peter Mortimer,[9] Shih-Yuan Lee,[8] Daniel George[10]

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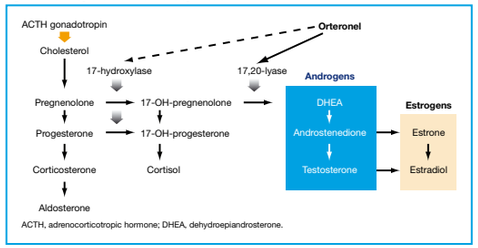
BACKGROUND

- Nonmetastatic, castration-resistant prostate cancer (nmCRPC) is an area of unmet medical need.[1–6]
- The only disease manifestation is rising prostate-specific antigen (PSA).[1]
- Median metastasis-free survival is ~30 months.[1]
  - One mechanism for castration resistance is the conversion of gonadal, adrenal, and tumoral androgen precursors to androgens, which results in tumor progression.[2–4]
- Orteronel (TAK-700) is an investigational, selective, non-steroidal inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones (Figure 1).
  - In preclinical studies, orteronel inhibited 17,20-lyase activity more than 17-hydroxylase, with IC_{50} values of 140 nmol/L (95% CI: 120, 170) and 760 (640, 910), respectively, with minimal effect on CYP drug-metabolizing enzymes.[7]
- Orteronel has limited inhibition of 17α-hydroxylase, and may have less effect on cortisol synthesis, reducing the potential for mineralocorticoid excess, and has potential to allow for steroid-free dosing, making orteronel an attractive drug for longer durations of therapy.

Figure 1. Pathway of steroid hormone synthesis



ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone.

OBJECTIVES

Primary:

- The percentage of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels) after 3 months.

Secondary:

- Safety of orteronel
- PSA response rates at 3 and 6 months (decline in PSA of ≥90%, ≥50%, and/or ≥30%)
- The percentage who achieve a PSA ≤0.2 ng/mL after 6 months
- Time to PSA progression, time to metastases, and duration of progression-free survival (PFS)
- Changes in endocrine markers: serum testosterone, ACTH, DHEA, leuteinizing hormone (LH), corticosterone, and cortisol concentrations.

Exploratory:

- Exploratory endpoints include analysis of circulating tumor cells (CTC).
- Other candidate biomarkers (not yet available).

METHODS

Key eligibility

Entry criteria:

- Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma without radiographic evidence of metastasis
- nmCRPC with progression as reflected by baseline PSA ≥2 ng/mL and a doubling time ≤8 months, or PSA ≥8 ng/mL with a doubling time >8 months
- ≥18 years of age
- Surgical or ongoing medical castration, with testosterone <50 ng/dL.

Exclusion criteria:

- Prior therapy with aminoglutethimide or ketoconazole
- Antiandrogen therapy within 4 weeks (flutamide) and 6 weeks (all others)
- Prior chemotherapy for prostate cancer other than in the adjuvant setting
- Radiation therapy for prostate cancer within 30 days prior.

Study design and treatment

- Orteronel 300 mg BID treatment without prednisone was evaluated in men with nmCRPC and rising PSA.
- Patients received orteronel at 300 mg BID in 28-day treatment cycles.
- Orteronel therapy was continued until PSA progression, metastases, or unacceptable toxicities.

Assessments

- Physical exam and radiologic evaluations (CT/MRI) at screening assessed underlying disease status at study entry.
  - Evaluated at cycle 4, 7, 10, 13, and every 4th cycle until end of treatment.
- Toxicity according to NCI-CTCAE v4.03.
- Serum PSA levels at screening, at day 1 of cycles 1–7, 10, 13, and every 3rd cycle until PSA progression.
- Adrenal function was assessed on day 1 of cycles 1–7, 10, 13, and every 6 cycles thereafter, and included plasma ACTH, serum cortisol, DHEA, LH, corticosterone, and testosterone.

Endpoint definitions

- Primary endpoint: The percentage of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels) after 3 months.
- PSA progression: A 25% increase over the baseline/nadir concentration on two consecutive measurements at least 1 week apart and an absolute PSA increase ≥2 ng/mL.
- PFS: Time from first dose to first PSA progression, metastasis or death.
- PSA response rate: Percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).
- Metastasis: ≥2 new lesions on bone imaging or 1 new lesion on soft tissue imaging.
- Time to metastasis: Time from first dose to first occurence of metastasis.

Statistical considerations

Sample size

- 38 patients provided 90% power to give a 1-sided significance level of 0.1 (H_0 5% vs. H_a 20%) for the percentage of patients achieving a PSA of ≤0.2 ng/mL after 3 months of orter onel treatment.

Population for analysis

- PSA response rate: patients with nmCRPC, PSA entry criteria, baseline and ≥1 post-baseline PSA measurement (N=38).
- Safety and time to event: patients with ≥1 dose of study drug (N=39).

Efficacy analysis

- Patients who achieve PSA of ≤0.2 ng/mL and had PSA assesments (PSA90, PSA50, PSA30).
- Time-to-event: Kaplan-Meier estimate of median, 6, and 12 month PFS.

RESULTS

- Data are presented as of December 15, 2011 and the study is currently ongoing.
- Patient demographics and disease characteristics are shown in Table 1.

Table 1. Baseline patient demographics

Characteristic	N=39
Median age, years (range)	71 (53–81)
Race (n, %)	
White	35 (90)
Black	4 (10)
ECOG performance status (n, %)	
0	33 (85)
1	6 (15)
Median (range)	
PSA	12.1 ng/mL (2.6–67.8)
Testosterone	7.9 ng/dL (1.4–17.3)
ACTH (n=33)	19.0 ng/L (0–47)

Safety

- Adverse events (AEs) were reported in 36 men (92%; Table 2).
- No grade 4 or 5 AEs were observed.
- 2 patients discontinued treatment for grade 2 adrenal insufficiency; upon review of the data, only 1 patient had laboratory values consistent with a hypoadrenal state.

Table 2. Most common treatment-emergent AEs reported in ≥20% of patients or grade 3 in ≥5% of patients

	Orteronel 300 mg BID (n=39)		
AE	All (n, %)	Grade 1/2	Grade 3
Fatigue	23 (59)	21 (54)	2 (5)
Diarrhea	15 (38)	14 (36)	1 (3)
Nausea	14 (36)	14 (36)	–
Hypertension	13 (33)	8 (21)	5 (13)
Decreased appetite	12 (31)	12 (31)	–
Constipation	11 (28)	11 (28)	–
Dyspnea	9 (23)	6 (15)	3 (8)
Cough	9 (23)	9 (23)	–
Vomiting	9 (23)	9 (23)	–
Dysgeusia	8 (21)	8 (21)	–
Dyspepsia	8 (21)	8 (21)	–
Hypokalemia	6 (15)	4 (10)	2 (5)
Pneumonitis	3 (8)	1 (3)	2 (5)

Serious AEs: 7 men (18%); 6 drug-related; most common pneumonitis (2 grade 3; 1 at grade 2); others included dyspnea, hypoxia, pulmonary embolism, atrial fibrillation, atrial flutter, adrenal insufficiency, and syncope (1 each). Discontinuations in 8 men due to AEs: dyspnea, pneumonitis, adrenal insufficiency, fatigue, hypertension (2 each), and diarrhea (n=1); 3 patients had dose reduction due to AEs: 1 patient due to left ventricular dysfunction, brain natriuretic peptide increased, sinus bradycardia, and atrioventricular block first degree; 1 patient due to diarrhea and vomiting; 1 patient due to fatigue and decreased appetite.

Treatment summary

- 17 men (44%) were on treatment for >6 months at the time of data cut-off.
- Median number of treatment cycles: 6 (range 1–17).

Efficacy summary

PSA response

- 6 men (16%) achieved PSA ≤0.2 ng/mL at 3 months.
- 32% of patients experienced a PSA90 at 3 months.
- 76% of patients experienced a PSA50 at 3 months.
- PSA response rate at 3 and 6 months of treatment are summarized in Table 3.
- Waterfall plot of maximum PSA change at any time on treatment is shown in Figure 2.
- Waterfall plots of PSA change at 3 and 6 months are shown in Figure 3.

Table 3. PSA response rate at 3 and 6 months

	3 months		6 months	
N=38	n (%)	(80% exact CI)	n (%)	(80% exact CI)
PSA ≤0.2ng/mL	6 (16)	(9, 26)	2 (5)	(1, 13)
PSA90	12 (32)	(22, 43)	8 (21)	(13, 32)
PSA50	29 (76)	(65, 85)	17 (45)	(34, 56)
PSA30	31 (82)	(71, 89)	20 (53)	(41, 64)

PSA response rate: percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).

Figure 2. Waterfall plot of maximum PSA response at any time on treatment

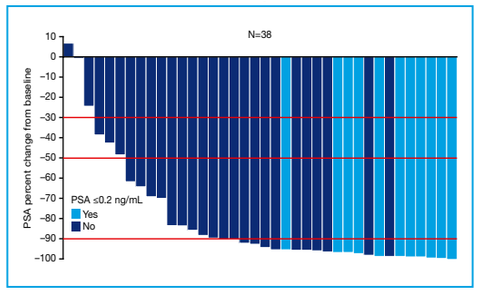
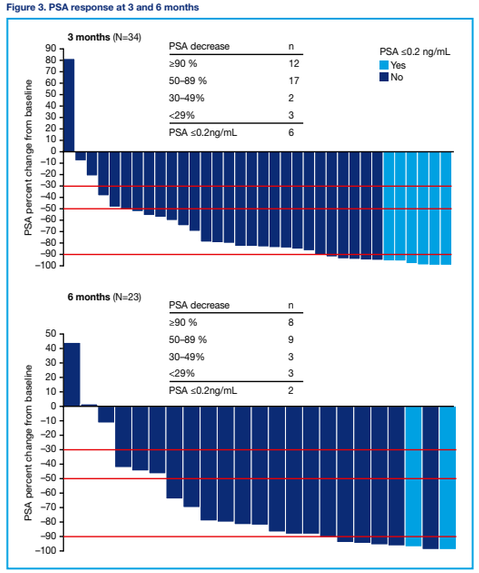


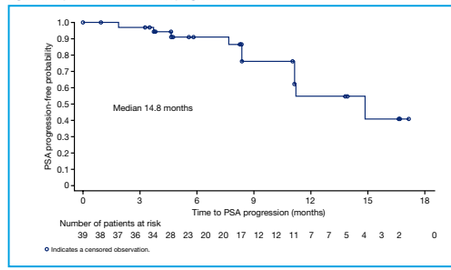
Figure 3. PSA response at 3 and 6 months



PSA progression

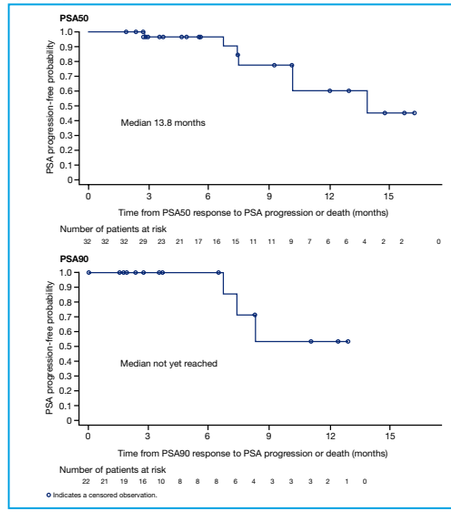
- Kaplan-Meier estimates of freedom from PSA progression were 97%, 91%, and 55% at 3, 6, and 12 months, respectively.
- Median time to PSA progression was 14.8 months (Figure 4).
- Duration of PSA response, as measured from time from first PSA response to protocol-defined PSA progression, is shown in Figure 5 for men who achieved PSA50 and PSA90 responses.

Figure 4. Kaplan-Meier time-to-PSA progression



Indicates a censored observation.

Figure 5. Kaplan–Meier duration of PSA50 and PSA90 response

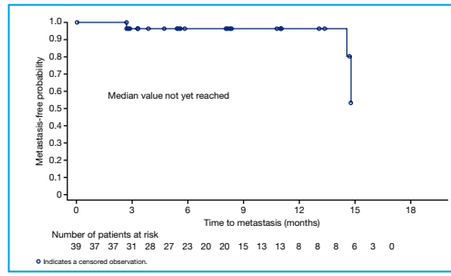


Indicates a censored observation.

Time to metastasis

- Kaplan-Meier estimates of freedom from metastasis is 97% for patients at 6 and 12 months (n=20, n=8, respectively, Figure 6).

Figure 6. Kaplan-Meier time to metastasis



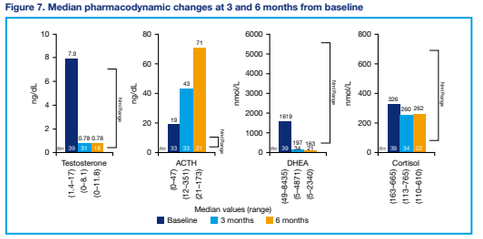
Indicates a censored observation.

Endocrine markers

- Pharmacodynamic responses for serum testosterone, DHEA, ACTH, and cortisol are shown in Figure 7.
  - Testosterone decreased by 88–89%.*
  - ACTH increased by ~2–3-fold.
  - DHEA decreased by 85–90%.
  - Cortisol decreased by 21–32%.

*Percent change from baseline is based on the number of patients with both baseline and post-baseline values at that cycle.

Figure 7. Median pharmacodynamic changes at 3 and 6 months from baseline



Circulating tumor cells

- 7 patients had ≥1 CTC at baseline assessment (Table 4).
  - 1 patient had ≥5 cells/7.5 mL at baseline and converted to <5 cells/7.5 mL at the 3, 6, and 12 month assessments.
  - No patients had ≥5 cells after baseline during orteronel treatment.

Table 4. CTC assessments

	Time of assessment			
	Baseline	3 months	6 months	12 months
Patients assessed (n)	36	33	21	9
Number of CTCs	Patients with CTCs (n)			
1–4 CTCs	6	2	1	0
≥5 CTCs	1	0	0	0

CONCLUSIONS

- In patients with nmCRPC and rising PSA, single agent oral orteronel at a dose of 300 mg BID without prednisone was feasible and had manageable toxicities.
- After 3 months of orteronel treatment, 16% achieved PSA ≤0.2 ng/mL.
  - 76% achieved ≥50% decrease in PSA and 32% achieved a PSA reduction of ≥90%.
- Median time to PSA progression was 14.8 months.
- With a median follow up of 6 cycles (5.5 months), only 3 patients developed systemic metastasis and median time to metastasis was not reached.
- Fatigue, diarrhea, and nausea were the most common AEs.
  - All AEs were grade ≤3.
- Orteronel without prednisone suppressed adrenal androgens (testosterone and DHEA) by 85–90%.
  - Although ACTH was increased, median cortisol levels were decreased and remained within the normal range.
  - Although 2 patients discontinued treatment for "adrenal insufficiency", only 1 had laboratory values consistent with a hypoadrenal state for which he received corticosteroid replacement.

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PC, HH, JA, CR, and JB have no conflicts to disclose
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APPENDIX G

Prostate Cancer and Prostatic Diseases (2012) 15, 87–92

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ORIGINAL ARTICLE

A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study

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BACKGROUND: Intermittent androgen suppression (IAS) is an increasingly popular treatment option for castrate-sensitive prostate cancer. On the basis of previous data with anti-angiogenic strategies, we hypothesized that pan-inhibition of the vascular endothelial growth factor receptor using pazopanib during the IAS off period would result in prolonged time to PSA failure.

METHODS: Men with biochemically recurrent prostate cancer, whose PSA was $<0.5\,ng\,ml^{-1}$ after 6 months of androgen deprivation therapy were randomized to pazopanib 800 mg daily or observation. The planned primary outcome was time to PSA progression $>4.0\,ng\,ml^{-1}$.

RESULTS: Thirty-seven patients were randomized. Of 18 patients randomized to pazopanib, at the time of study closure, 4 had progressive disease, 1 remained on treatment and 13 (72%) electively disenrolled, the most common reason being patient request due to grade 1/2 toxicity (8 patients). Two additional patients were removed from treatment due to adverse events. Of 19 patients randomized to observation, at the time of study closure, 4 had progressive disease, 7 remained under protocol-defined observation and 8 (42%) had disenrolled, most commonly due to non-compliance with protocol visits (3 patients). Because of high dropout rates in both arms, the study was halted.

CONCLUSIONS: IAS is a treatment approach that may facilitate investigation of novel agents in the hormone-sensitive state. This trial attempted to investigate the role of antiangiogenic therapy in this setting, but encountered several barriers, including toxicities and patient non-compliance, which can make implementation of such a study difficult. Future investigative efforts in this arena should carefully consider drug toxicity and employ a design that maximizes patient convenience to reduce the dropout rate.

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Keywords: intermittent androgen suppression; tyrosine kinase inhibitors; pazopanib randomized consortium trial

Introduction

The importance of androgen deprivation for treatment of prostate cancer has been known since the 1940s.[1,2] Over the past 70 years, many novel and highly effective treatments have been introduced; however, continuous androgen suppression (CAS) currently remains the standard of care for men with hormone-sensitive metastatic disease. Intermittent androgen suppression (IAS)[1] is a concept that advocates alternating periods of treatment with and without androgen suppression. The body of literature which supports its use is growing.[3–T4] Preliminary results of an ongoing multicenter, randomized, controlled phase III trial comparing IAS and CAS in a population of patients with biochemical recurrence following local therapy (NCIC PR7) were recently presented; they demonstrated that IAS was non-inferior to CAS with a mean overall survival of 8.8 years and 9.1 years, respectively (hazard ratio = 1.02, 95% confidence interval = 0.86–1.21; *P*-value for non-inferiority (hazard ratio for IAS vs CAS > 1.25) = 0.009). IAS patients had fewer hot flashes. Quality-of-life data are not yet evaluable.[15]

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Several investigators have proposed ways to increase the 'off' period of IAS, with the hypothesis that this could improve treatment efficacy, and possibly even decrease long-term androgen deprivation therapy (ADT) toxicities. One class of medications under investigation for this purpose are angiogenesis inhibitors.[16–21] Elevated plasma and urine vascular endothelial growth factor (VEGF) levels have been correlated with shortened survival times in men with hormone refractory disease,[22,23] leading to the hypothesis that anti-angiogenesis agents may have a role in prostate cancer treatment. *In vivo* models using Shionogi mice have shown that castration leads to a regression in the size of androgen-dependent tumors that is coupled with a decrease in VEGF expression;[24] however, when tested, anti-angiogenesis agents have not yet demonstrated survival benefits in men with prostate cancer.

Pazopanib is an orally available multi-targeted tyrosine kinase inhibitor with broad activity against VEGF receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α, PDGFRβ, and c-kit among others,[25] and is a standard available therapy for advanced renal cell carcinoma.[26] In this randomized, phase II study, we tested the hypothesis that pazopanib could prolong the 'off' period of IAS.

Materials and methods

Study objectives

The primary objective was to determine if pazopanib was able to increase time to PSA progression (TTPP) following 6 months of androgen blockade in patients with stage D0 prostate cancer. Secondary objectives were to describe progression-free survival and adverse events (AEs) related to pazopanib in this population, as well as to monitor and compare changes in testosterone in the two treatment arms.

Patients and eligibility criteria

Eligible patients had pathologically confirmed prostate cancer, had received definitive local therapy and had evidence of biochemical recurrence, defined as two consecutive rises in PSA above the nadir, following definitive local therapy. Patients with radiologically detectable disease were excluded, which was confirmed with a bone and CT scan if the baseline PSA level was greater than 10 ng ml^{-1}. Prior ADT was disallowed. All patients had an Eastern Cooperative Oncology Group performance status $\leqslant 2$, normal renal and hepatic function as defined by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE 3.0), as well as a urine protein to creatinine ratio of <1.

Patients were excluded if they had uncontrolled hypertension ($>140/90$ mm Hg), New York Heart Association class III or IV heart failure, a history of cerebrovascular accident, myocardial infarction, unstable angina, or coronary artery stenting within 6 months of enrollment, or a history of venous thrombosis within 12 weeks of enrollment. Patients who required treatment with strong CYP450 3A4 inhibitors or inducers were not allowed to participate. Other exclusion criteria included inability to take oral medications and patients with HIV on anti-retroviral therapy.

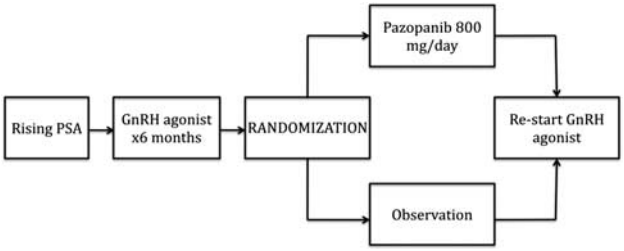


Figure 1 Schema for the randomized, placebo-controlled, phase II study.

Study design

This study employed a multicenter, two-arm, randomized, phase II design. Each center's Institutional Review Board approved the investigational protocol and all subjects provided written informed consent in accordance with the Helsinki Declaration of 1975. The study schema is depicted in Figure 1. Upon verification of eligibility, subjects were enrolled and completed a period of 6 months of androgen blockade with a gonadotropin-releasing hormone agonist without concomitant anti-androgen therapy. At this time, if the subject's PSA was <0.5 ng ml^{-1} and total serum testosterone level was <50 ng ml^{-1}, he was randomized to treatment with pazopanib 800 mg daily or observation.

The primary endpoint was TTPP, which was measured as the time from randomization until the total serum PSA was >4.0 ng ml^{-1}, with non-cancer and non-treatment-related deaths censored. The secondary endpoint was progression-free survival, defined as the time from randomization until the time of PSA progression or death from any cause. Subjects were seen monthly with physical examination, history, PSA and testosterone evaluation. Subjects remained on either pazopanib or active surveillance until they met the TTPP criteria withdrew consent, or were removed by the investigator for adverse events or other reasons.

Subjects were monitored for toxicity on a monthly basis, and adverse events were classified according to the CTCAE v3.0. All patients measured their blood pressure on a twice-daily basis while on trial and maintained a blood pressure diary. Specific guidelines were provided for management of treatment-associated hypertension, transaminitis and proteinuria. All subjects were followed for 12 months after disenrollment from the study for toxicity evaluation.

Statistical analysis

The study was designed to achieve 85% power to detect a difference of 5 versus 9 months in the median TTPP between the two study treatment groups at the one-sided 0.10 significance level, allowing for a 15% rate of non-cancer deaths. This required a sample size of 94 patients, 47 in each arm. The planned statistical analysis included calculating the Kaplan–Meier estimates of the primary endpoint, TTPP, as well as the secondary endpoint of progression free survival, and comparison of TTPP and

progression free survival between the two treatment arms using the log-rank test.

Table 1 Baseline patient characteristics

	Observation (n = *19*)	*Pazopanib* (n = *18*)
Primary Gleason score	3.63 (s.d. 0.50)	3.61 (s.d. 0.70)
Secondary Gleason score	3.63 (s.d. 0.68)	3.61 (s.d. 0.70)
Stage		
⩾T3	66.7% (10/15 pts)	41.7% (5/12 pts)
⩽T2	33.3% (5/15 pts)	58.3% (7/12 pts)
Primary therapy		
Surgery	94.7% (18/19 pts)	72.2% (13/18 pts)
Radiotherapy	5.3% (1/19 pts)	27.8% (5/18 pts)
Pre-ADT treatment PSA ($ng\,ml^{-1}$)	3.29 (s.d. 2.94)	11.09 (s.d. 15.03)
Undergoing salvage radiotherapy %	78.9 (15/19 pts)	52.9 (9/17 pts)

Abbreviations: ADT, androgen deprivation therapy; pts, patients.

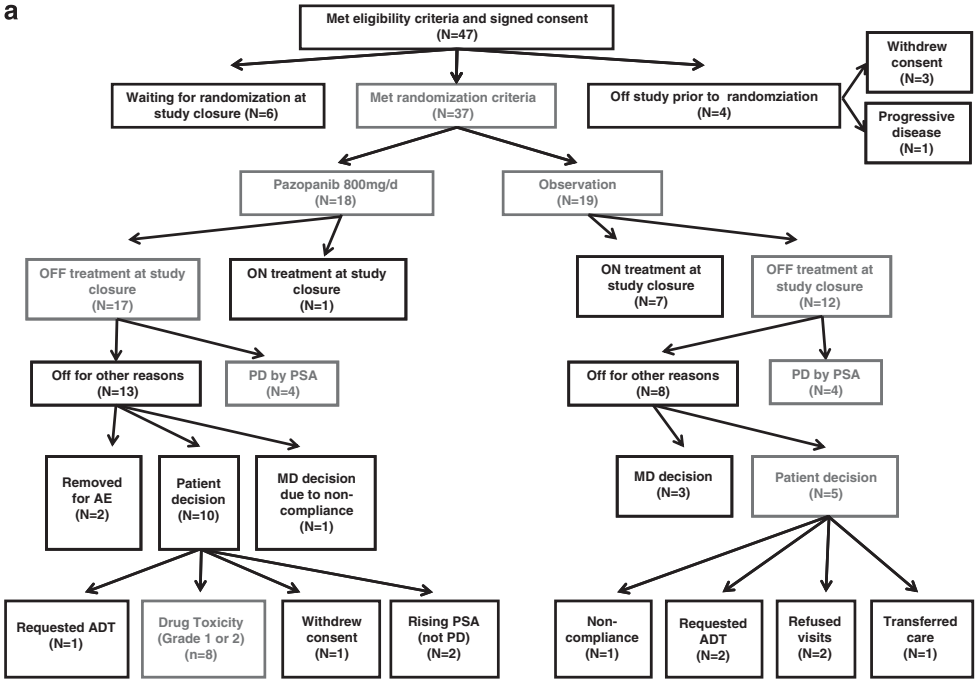
Results

Patient data and treatment outcomes

Baseline patient characteristics are shown in Table 1. There were no statistically significant differences between the treatment arms in any of the relevant categories at the $\alpha = 0.05$ level. Because of high patient dropout, early closure was recommended by the Data Safety and Monitoring Board, as it was no longer possible to validly test the primary hypothesis. At the time that the study was stopped, 37 patients had been randomized, 18 to pazopanib and 19 to observation. We report here the findings from these 37 evaluable patients.

A flowchart outlining the reasons for subject disenrollment is provided in Figure 2a. Seventeen of the 18 patients randomized to the pazopanib arm were off treatment at the time of study closure. Four of the 18 patients (22%) reached the primary endpoint of PSA progression. Thirteen of the 18 patients went off study for other reasons. Two of the 18 (11%) patients were removed for an AE; one patient sustained a pulmonary embolism (Grade 4) and one showed recurrent grade 2 hepatotoxicity, despite dose adjustment. An additional patient was

a



b

	PAZOPANIB	OBSERVATION
Reached study endpoint: PD	22.0% (4/18 pts)	21.0% (4/19 pts)
Off study for other reasons	72.0% (13/18 pts)	42.0% (8/19 pts)
Disenrolled due to drug side effects	44.4% (8/18 pts)	0.0% (0/19 pts)
Disenrolled due to study related visits/rules	16.7% (3/18 pts)	26.3% (5/19 pts)

Figure 2 (**a**) Flowchart of patient accrual and reasons for study discontinuation. (**b**) Patient outcomes including most common reasons for study discontinuation. ADT, androgen deprivation therapy; AE, adverse effects; Pts, patients.

Table 2 Reported adverse events including most commonly occurring toxicities[a]

Event	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total*
No. of events	67	27	12	1	107
Diarrhea	8	3	2	—	13
Fatigue	6	3	—	—	9
Hypertension	2	2	3	—	7
↑ ALT	3	2	2	—	7
↑ AST	5	1	1	—	7

[a]All adverse events reported here (attribution ⩾3, possibly, probably or definitely related to treatment) were documented in the pazopanib arm.

removed by a study investigator due to non-compliance (undiagnosed pre-existing dementia, unrelated to treatment). Ten patients withdrew consent, including eight patients (44%) due to drug toxicity (Grades 1–2). Of these eight patients, four withdrew in less than 2 months, another three withdrew between 2–6 months, and one patient withdrew after 18 months. One patient requested further treatment with ADT and one patient did not provide a reason for withdrawal of consent.

Of the 19 patients who were randomized to the observation arm, 12 (63%) were off treatment at the time of study closure. Four patients out of 19 (21%) met the primary endpoint of PSA progression. Three patients (16%) were removed by the study investigators, including one for non-compliance. Five patients (26%) withdrew consent, including two patients who requested further treatment with ADT, two patients who refused study-related visits, and one patient who transferred care. Including the one patient removed by study investigators due to non-compliance, five patients (26%) in this treatment arm left the study due to issues surrounding the study protocol. All five of these patients left or were removed from the study within 5 months of randomization. Patient outcomes are summarized in Figure 2b.

Toxicity data

All AEs were classified according to CTCAE 3.0. The number and grade of the AEs recorded during the study period are listed in Table 2. All of these were in patients receiving pazopanib. No AEs designated as possibly, probably or definitely related to the treatment were observed in the observation arm. There were a total of 12 grade 3 AEs in 10 patients: 3 patients with hypertension, 2 patients each with diarrhea and increased ALT, and 1 patient each with increased AST, anorexia, hypophosphatemia, hyponatremia and dizziness. There was one grade 4 event, a pulmonary embolism. The most commonly occurring AEs (Table 2) were diarrhea, hypertension, increased ALT and increased AST, each with a maximum documented grade of 3 and fatigue, with a maximum grade of 2.

Discussion

IAS is an emerging standard of care for biochemically recurrent prostate cancer and has been proposed as a useful clinical model for developing novel agents in castrate-sensitive prostate cancer. Because the re-growth of cancer during the off period is presumably accompanied by angiogenesis,[24] angiogenic inhibitors in general and VEGF pathway inhibitors specifically have been hypothesized to be useful in this setting. We undertook a randomized phase II trial with the VEGFR tyrosine kinase inhibitor pazopanib to test this hypothesis.

Unfortunately and somewhat unexpectedly, the high dropout rate in both arms of this trial made measurement of the primary outcome at the planned power and significance levels infeasible. The most common reason for dropout in the pazopanib arm was drug-related toxicity (across all grades) accounting for 44% of these patients. The toxicity was predominantly grade 1 or 2 by convention. Compared with published data of pazopanib in advanced renal cell carcinoma, the frequency and severity of toxicities noted in this study were similar and yet the dropout rate was substantially higher, 44.4 versus $<6\%$ in the pazopanib arm and 26.3 versus $<3\%$ in the control arm.[26] Studies of other VEGFR inhibitors in patients with castrate-resistant prostate cancer have mostly demonstrated similar toxicities without the same issues of patient drop out. One such phase II study of sunitinib in patients with mCRPC in the post-chemotherapy setting did have significant patient dropout (52.8%).[27] However, an ongoing phase II study, as well as a completed phase II study of sunitinib in patients with castrate-resistant disease did not report the same difficulties with patient dropout, despite a similar toxicity profile.[1,28] Several phase II studies of sorafenib in patients with castrate-resistant disease also did not report high levels of patient dropout.[21,29,30] To our knowledge, however, VEGFR inhibitors have not been studied in the setting of biochemical recurrence, nor has mature data of pazopanib in prostate cancer been presented.

The fact that this trial had higher dropout rates than other studies with pazopanib or other members of this drug class, despite similar toxicity data, suggests a lower tolerance for drug-related AEs in the setting of IAS. Patients on the off period of IAS suffer fewer adverse effects (hot flashes),[15] and these data suggest it is reasonable to conclude that this population of patients has an expectation for lower treatment-related toxicity and thus, has a higher likelihood to dropout of clinical studies due to treatment related adverse events. The currently used CTCAE classification system may be appropriate for reporting severity of toxicity and the danger patients experience on treatment. However, dose adjustment guidelines based on these criteria cannot be uniformly applied across tumor models and across the spectra of health states that exist within tumor models. Simply stated, a patient with hormone-sensitive prostate cancer with no symptomatology has presumably less incentive to endure the same level of toxicity or adhere to a prescribed visit schedule as a patient with advanced renal cell carcinoma appropriate for medical intervention. This conclusion is bolstered by the finding in this study that patients in the observation arm also dropped out at a higher than expected rate, despite recruitment at centers with expertize and experience in accruing to trials with both novel therapeutic agents and intermittent hormonal therapy. The most common reason for patient dropout, occurring in 26% of the patients in this arm of the study, was due to protocol-related visits and procedures.

The experience of patients in this study provides an important lesson. Given the preliminary results of the

National Cancer Institute of Canada PR7 study,[15] it is likely that the usage of IAS as a therapeutic strategy for men with castrate-sensitive prostate cancer will grow. It follows that future clinical trials will continue to investigate new therapies with the goal of lengthening TTPP, thus allowing for longer periods of time-off of ADT during IAS. This study indicates that patients within this population have a low threshold for drug-related toxicity and protocol-related visits and procedures. Future trial design within this therapeutic niche should take these results into consideration.

Conflict of interest

Dr Posadas has received compensation from GlaxoSmithKline as a member of their speaker's bureau. Drs Ward, Karrison, Chatta, Hussain, Shevrin, Szmulewitz, O'Donnell and Stadler have nothing to disclose.

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